

EDITORIALS

Three Roots of Melanoma

SEGURA ET AL¹ DESCRIBE MORPHOLOGIC FEATURES of melanomas with a nodular component using in vivo reflectance-mode confocal microscopy (RCM) and correlate these RCM findings with histopathologic findings. The most striking observation made by the investigators is the remarkable difference in epidermal

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involvement between nodular melanoma (NM) and superficial spreading melanoma (SSM) with a nodular component. At RCM, SSMs frequently showed epidermal disarrangement and pagetoid infiltration, whereas NMs exhibited a preserved epidermal pattern and few paget-

oid cells.¹ This new observation provides fertile ground for revisiting the conventional concept of melanoma development. We propose an alternative hypothesis based on recent observations made in stem cell research and demonstrate how this hypothesis can better account for the observed clinical and epidemiologic differences between melanoma subtypes.

Many clinicians and researchers subscribe to the theory that all cutaneous melanomas arise from transformed epidermal melanocytes. The malignant cells are thought to initially proliferate along the basal layer (melanoma in situ). After a variable period, which can range from months to decades, the malignant melanocytes may acquire the capacity to not only proliferate radially but also invade

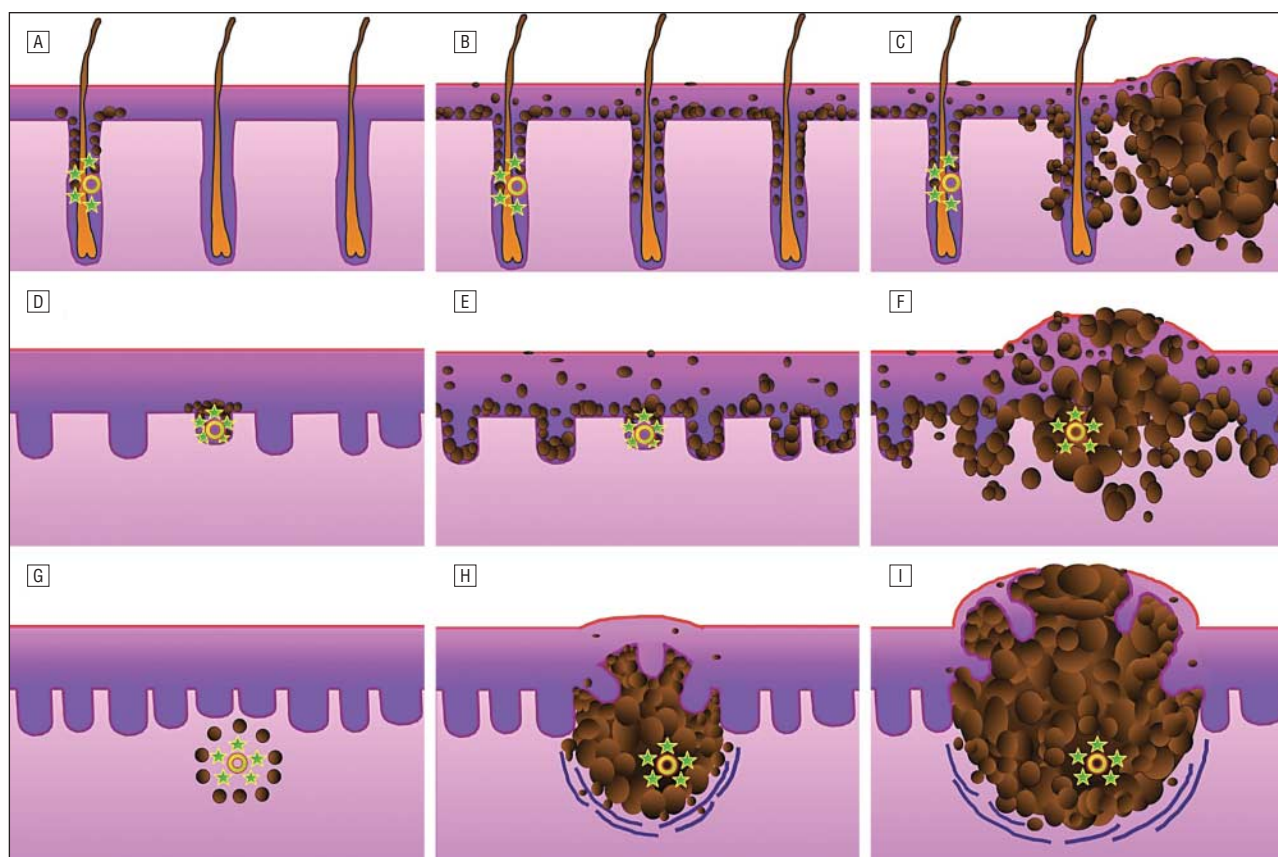


Figure 1. Schematic model shows the origin of lentigo maligna, nodular melanoma, and superficial spreading melanoma from melanoma stem cells of the hair follicle, the dermis, and the epidermal basal layer, respectively. Melanoma stem cells (yellow concentric ring) produce progenitor cells (green stars) that drive proliferation and progression of melanoma cells (brown circles). A-C, Lentigo maligna deriving from stem cells of the outer sheet of the facial hair follicle. D-F, Superficial spreading melanoma deriving from stem cells in the epidermal basal layer. G-I, Nodular melanoma deriving from dermal stem cells.

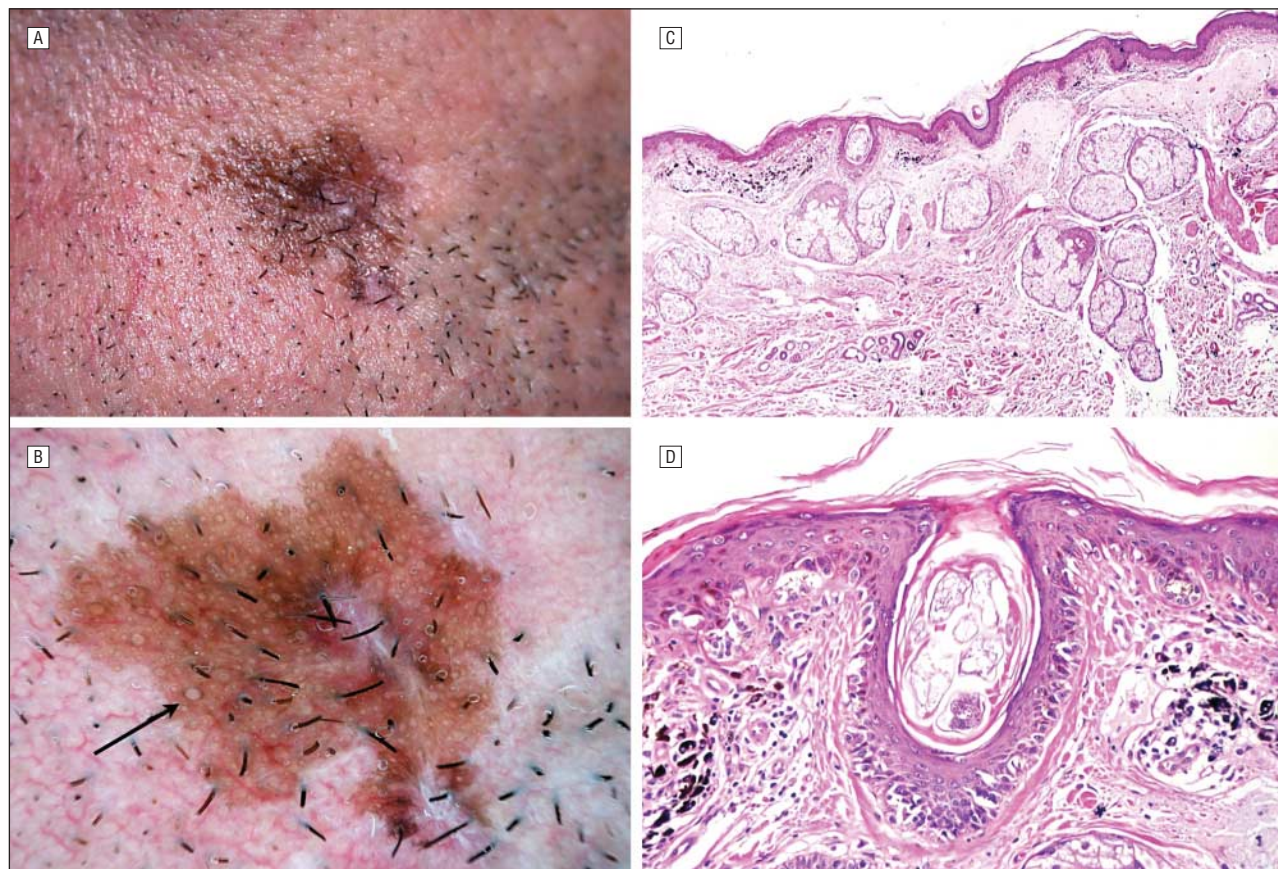


Figure 2. Lentigo maligna. A, Clinical appearance. B, Dermoscopic examination revealed asymmetric pigmented hair follicles as the earliest sign of tumor growth (arrow) (original magnification $\times 10$). C, At histopathologic analysis, melanocytes are arranged in nests and single units at the dermoepidermal junction. The papillary dermis exhibits solar elastosis, scattered melanophages, and a sparse lymphoid infiltrate (hematoxylin-eosin, original magnification $\times 40$). D, Note the prominent perifollicular arrangement of melanocytes at higher magnification (hematoxylin-eosin, original magnification $\times 200$).

vertically into the dermis (invasive melanoma). The rapidity with which melanoma can invade the dermis probably depends on multiple factors including the proliferative rate of the tumor cells, the degree of neoangiogenesis, and the ability of the surrounding tumor microenvironment to permit or impede the migration of malignant cells.² Based on clinical observations of the rate of growth of melanomas, most melanomas can be categorized into 1 of 3 groups: very slow growing (ie, lentigo maligna [LM]), slow growing (ie, SSM), and fast growing (ie, NM).³

However, the theory of epidermal origin of melanoma cannot adequately explain the absence of substantial epidermal involvement (ie, lack of pagetoid spread) and lack of a radial component (ie, radial spread confined to within 3 rete ridges at either edge of the tumor) in NM.¹ It is presumed that the malignant melanocytes in NM proceed directly to rapid vertical growth while being incapable of horizontal growth, perhaps owing to inherent properties of the malignant cells or the tumor microenvironment. These distinctive properties of NM cells are poorly understood. Furthermore, it is virtually impossible for the epidermal origin of melanoma theory to account for the origin of primary dermal melanomas.^{4,5}

Thus, it behooves us to explore an alternative hypothesis that explains the origin and growth characteristics of the different subtypes of melanoma. To this end, stem

cell research has opened up new and intriguing horizons that may enable better understanding of development of cancer in general and melanoma in particular.⁶⁻⁹ Stem cells are slowly proliferating self-renewing cells that are able to differentiate into cell types of multiple lineages (ie, multipotent stem cells) or of one lineage (ie, unipotent stem cells). Researchers have identified stem cells of melanocytic lineage in the human hair follicle, the epidermis, and recently also in the dermis.¹⁰⁻¹² Emerging evidence supports the theory that some cancers such as breast cancer, melanoma, glioblastoma, and myeloid leukemia may arise from transformed stem cells.^{10,11} This stem cell-derived cancer model purports that malignant tumors are composed of relatively few cancer stem cells that constantly renew themselves, thereby helping to maintain a lifelong stem cell pool. In addition to self-renewal, stem cells also differentiate into rapidly proliferating transient amplifying cells or progenitor cells, which in turn differentiate into the mature cancer cells with limited proliferative potential.¹³

On the basis of the stem cell-derived cancer model and the notable clinical, morphologic, and epidemiologic differences among various subtypes of melanoma, we hypothesize that different melanomas arise from distinct types of cutaneous stem cells. We speculate that LM, NM, and SSM derive from melanoma stem cells of the outer sheet of the hair follicle, the dermal compart-

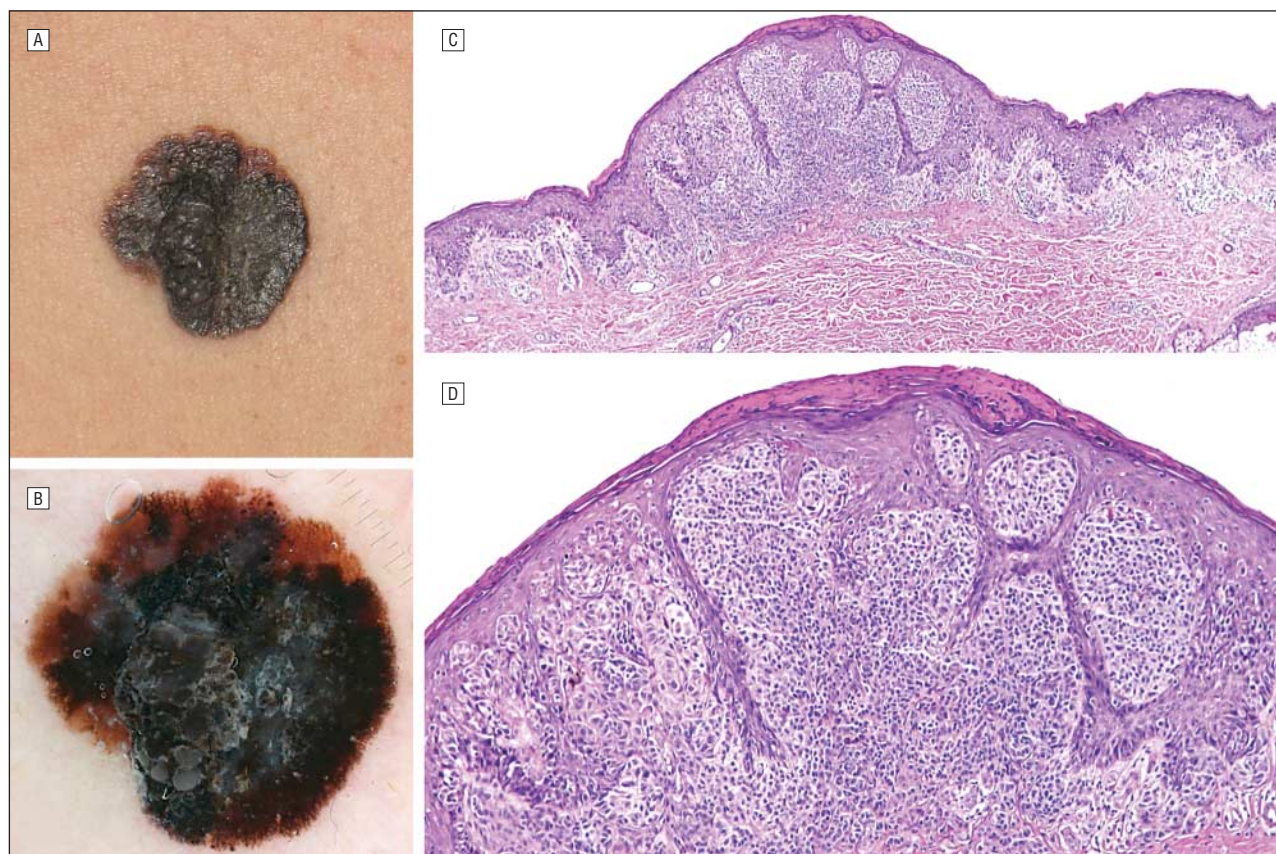


Figure 3. Superficial spreading melanoma. A, Clinical appearance. B, Dermoscopic examination exhibited a clearly discernible flat area around the nodular part. The flat area shows a pigment network that corresponds histopathologically to melanocytes along the rete ridges of the basal layer (original magnification $\times 10$). C, At histopathologic analysis, secondary nodular superficial spreading melanoma exhibits a broad melanoma in situ component with atypical melanocytes in nest and single cell formations within all epidermal layers, surrounding a central nodular melanoma component (hematoxylin-eosin, original magnification $\times 40$). D, Note the atypical melanocytes in higher layers of epidermis (pagetoid spread) above a nodular melanoma component (hematoxylin-eosin, original magnification $\times 100$).

ment, and the epidermal basal layer, respectively (**Figure 1**).

Chronic or intermittent sun exposure is widely accepted to have a crucial role in the development of LM and SSM, respectively, but does not seem to be a key event in the pathogenesis of NM. Studies have shown that NMs tend to develop in individuals who otherwise do not have obvious melanoma risk factors such as a family history of melanoma. These patients tend to manifest only few nevi, freckles, and actinic keratoses¹⁴; freckles are an accepted indicator of sun exposure. To explain the basis for the different phenotypic traits in patients with NM and the distinct morphologic appearance and biological behavior of NM, we hypothesize that melanocytic stem cells residing in the dermis, a location that receives negligible amounts of UV radiation, undergo spontaneous mutations that lead to the development of NM (**Figure 1**). The concept that NM originates in the dermis also explains why melanomas arising in large congenital nevi, whose melanocytic population extends deeply into the dermis and subcutis, are often nodular and subepidermal in origin. In contrast, stem cells in the hair follicles of chronically sun-exposed skin and in the epidermis of intermittently sun-exposed skin are at higher risk for acquiring UV-induced mutations, leading to development of LM and SSM, respectively.

In vivo observations at dermoscopy and reflectance-mode confocal microscopy (RCM) have provided further support for the concept that LM, NM, and SSM have different origins. At dermoscopy, pigmented dots around the hair follicles or the presence of asymmetric pigmented hair follicular openings are the earliest signs of LM (**Figure 2**), which suggests the follicular origin of LM.¹⁵ The morphologic hallmark of early SSM in situ is a pigment network pattern, which corresponds histopathologically to an increased number of melanocytes at the basal layer (**Figure 3**) and underscores an epidermal origin for this melanoma subtype.¹⁶

The study by Segura et al¹ in this issue of the *Archives* is of particular interest because it lends support to our hypothesis by showing important differences between NM and SSM with secondary invasive nodular components using RCM. In their study, NMs exhibited relatively minor pagetoid spread within a relatively preserved epidermal architecture, in contrast to epidermal disarrangement and abundant pagetoid infiltration observed in nodules occurring in SSMs. Similar findings are also seen at histopathologic analysis, revealing only few scattered epidermal melanocytes over the dermal tumor mass in NM (**Figure 4**) in contrast to the marked epidermal disarray and the striking pagetoid spread above the nodular component in SSM (**Figure 3**).

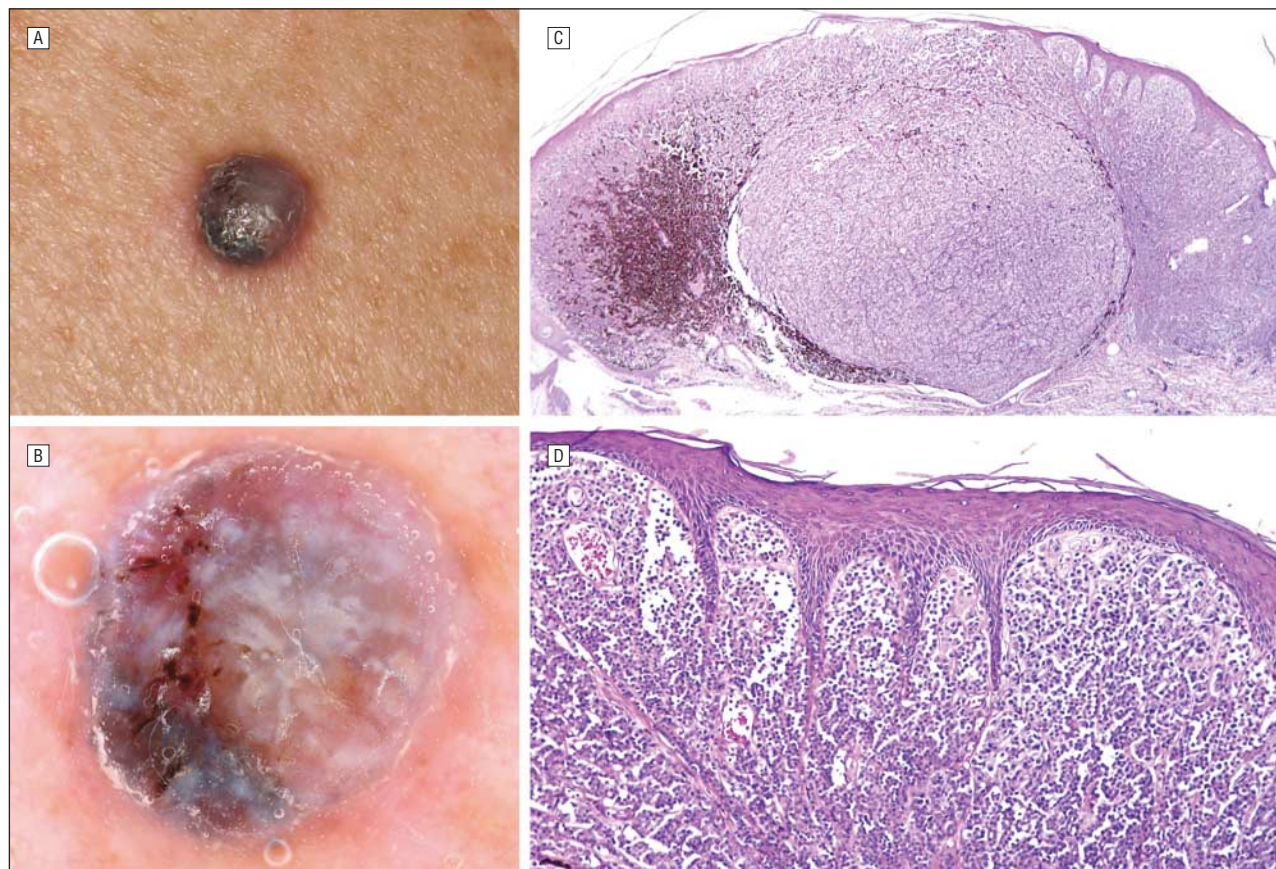


Figure 4. Nodular melanoma. A, Clinical appearance. B, Dermoscopic view. In contrast to the melanoma shown in Figure 3, no lateral flat part or pigment network structures are seen (original magnification $\times 10$). C, At histopathologic analysis, nodular melanoma consists of sheets of atypical melanocytes in the papillary and reticular dermis with asymmetric distribution of melanophages (hematoxylin-eosin, original magnification $\times 20$). D, Note the lack of intraepidermal melanocytes (hematoxylin-eosin, original magnification $\times 200$).

We have hypothesized that NM is derived from dermal stem cells and that the other melanoma subtypes are derived from epidermal stem cells. However, to better understand why NM grows much more rapidly than LM or SSM¹⁴ requires appreciation of the interaction of melanoma cells with surrounding cells and the tumor microenvironment. As Lee and Herlyn stated, "An often overlooked facet of tumor biology research is the involvement of the surrounding tumor microenvironment. Increasing evidence is being presented to support a major role for stromal components in all stages of tumorigenesis including initiation, progression, and metastasis."^{17(p862)} Under normal conditions, proliferation of epidermal melanocytes is controlled by the surrounding keratinocytes.¹⁸ It is plausible that during the early stages of melanoma development, proliferation of melanoma cells is slowed by relatively intact keratinocyte-melanocyte interactions. In contrast, keratinocytes are less likely able to regulate the proliferation of NM cells arising in the dermis. In addition, difference in the composition of the dermal stroma may further modify the rate of growth of LM, NM, and SSM.¹⁹

In conclusion, evidence is mounting that different melanoma subtypes may arise from distinct stem cells. However, further basic science and clinical research is

required to help elucidate the exact origin of the different melanoma subtypes.

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Type I Interferon in the Induction or Exacerbation of Dermatomyositis

What This Observation Tells Us About the Naturally Occurring Disease

ADVERSE EVENTS ASSOCIATED WITH MEDICATION use are a bane for physicians. However, when an adverse effect goes beyond an isolated clinical or laboratory finding and is instead a phenocopy of a naturally occurring disease state, we are presented with an opportunity to understand disease pathogenesis. The less common situation in which a disease state is reproduced with a naturally occurring biologic substance (ie, cytokine or hormone) makes even the most jaded of clinicians stand up and take note. The association of supraphysiologic amounts of an endogenous molecule with

differentiation, proliferation, apoptosis, and more.³ There are 3 classes of IFNs, all of which are highly conserved in vertebrates. Type I IFNs are a family of highly related proteins consisting of (in humans) IFN- α (13 subtypes), IFN- β , IFN- ω , IFN- ϵ , and IFN- κ .⁴ They all seem to signal via the same receptor, the type I IFN receptor (IFNAR); therefore, their activities are similar (potential differences in binding location and affinity might account for small distinctions between the various members). Virtually every cell is capable of producing type I IFN, consistent with its activity as a first-line agent for defense against viruses. This is in contrast to type II IFN (IFN- γ), which is mainly produced by natural killer cells and activated T cells. Type III IFNs are a newly discovered class consisting of 3 members, IFN- λ 1, IFN- λ 2, and IFN- λ 3, which have overlapping activities with type I IFNs but signal through a distinct receptor.⁴

The first interferon to be used in clinical medicine was interferon alfa, introduced in 1986 for the treatment of hairy cell leukemia.⁵ Today, preparations of interferon alfa and interferon beta are used for chronic viral hepatitis B and C, Kaposi sarcoma, Behçet disease, chronic myelogenous leukemia, multiple myeloma, multiple sclerosis, and carcinoid syndrome, to name just a few. Most of us are familiar with the more common “flu-like” symptoms associated with interferon use, including fever, malaise, myalgias, and the like. In addition, other nonspecific rashes are observed following exposure to interferon, including eczematous, lichenoid, vesicular, and ulcerative lesions. Germane to this discussion, however, is the association

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an induced disease state hardly provides physiologic proof of its connection in the spontaneously occurring disease, but it provides another level of evidence in a world in which the study of human disease rarely affords one with the opportunity to perform an in vivo experiment. It is with this level of interest and caution that we should approach the article in this issue of the *Archives* by Soman et al,¹ in which the administration of interferon beta is associated with new-onset dermatomyositis.

It has been more than 50 years since the discovery of interferon (IFN) as an endogenously produced substance with potent antiviral properties.² It is now clear that IFNs are proteins that have a more general role in innate and adaptive immunity, activating dendritic cells and lymphocytes in the fight against many types of infection, as well as having important roles in cellular